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A Systematic Review and Quantitative Meta-Analysis of Oxytocin's Effects on Feeding

Short Title: A systematic review of oxytocin's effects on feeding

Authors:

Leslie, Monica^a;

Silva, Paulo^a;

Paloyelis, Yannis^a;

Blevins, James^b;

Treasure, Janet^a

Affiliations:

^a Institute of Psychiatry, Psychology and Neuroscience (IoPPN) - King's College London (KCL), London, United Kingdom

^b VA Puget Sound Health Care System, Office of Research and Development Medical

Research Service, Department of Veterans Affairs Medical Center, Seattle, WA 98108, USA;

Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA 98195, USA

Corresponding Author: Monica Leslie – monica.leslie@kcl.ac.uk; - 103 Denmark Hill,

Section of Eating Disorders, London SE5 8AZ, United Kingdom

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Abstract

Purpose: Oxytocin's anorexigenic effects have been widely documented and accepted; however, no paper has yet used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to compile previous findings in a single systematic review and quantitative meta-analysis. The current paper aimed to identify published and unpublished studies examining the effects of oxytocin on energy intake in animals and humans, and the factors that moderate this effect.

Methods: Web of Science, Pub Med, and Ovid were searched for published and unpublished studies reporting the effects of oxytocin on energy intake in wild-type animals and in humans, when administered in the absence of other active drugs or surgery.

Results: 2049 articles were identified through the original systematic literature search, from which 54 articles were identified as relevant for inclusion in this review. An additional 3 relevant articles were identified in a later update of the literature search. Overall, a single-dose of oxytocin was found to reduce feeding in animals. Despite several individual studies which found that this effect persists to the end of the third week of chronic administration in rodent models, overall, this anorexigenic effect did not hold in the meta-analyses testing the effects of chronic administration. There was no overall effect of oxytocin on energy intake in humans, although a trend was identified for oxytocin to reduce consumption of solid foods.

Conclusions: Oxytocin reduces energy intake when administered as a single dose. Oxytocin can inhibit feeding over two- to three-week periods in rodent models. These effects typically do not persist beyond the third week of treatment. The anorexigenic effect of oxytocin is moderated by pregnant status, dose, method of administration, and diet composition.

KEYWORDS: OXYTOCIN; ENERGY INTAKE; FEEDING; ANIMALS; HUMANS

Introduction

Verbalis and colleagues ² and Kirchgessner³ first proposed a link between oxytocin and the control of food intake almost 30 years ago; which was subsequently corroborated by the Arletti lab ¹. Today, oxytocin has a well-established and well-accepted role in reducing food intake in rodents, although these effects have been found to be conditional on several factors ⁴.

The reported inhibitory effect of oxytocin on feeding has taken on new relevance in the face of the high prevalence of obesity in developed countries ⁵ and recognition of the psychological and functional difficulties faced by individuals with binge-type eating disorders, including bulimia nervosa and binge eating disorder ^{6, 7}. It has, accordingly, been proposed that oxytocin may be a useful supplement to administer to counter overeating and obesity ^{8, 9}.

In recent years, several narrative reviews have examined the role of oxytocin in a variety of functions related to the homeostasis of energy status: including its effects on feeding, energy expenditure, lipolysis, glucose homeostasis, and macronutrient preference ⁹⁻¹², as well as its potential to regulate disordered eating in humans ¹³. However, systematic reviews and meta-analyses in the style of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines are not commonly used in neurobiology and have not been previously used to estimate the size of the effect of oxytocin on feeding, and its possible moderators. This systematic method offers benefits such as the reproducibility, accountability of the search methods used, and quantitative precision in the measurement of effect size across different samples ¹⁴. De Vries and colleagues have therefore adapted similar guidelines for systematic reviews of animal intervention studies in order to bring these same benefits in methodical rigor to animal research ¹⁵.

The current paper therefore aimed to use this rigorous methodology to synthesize oxytocin's effects on feeding. We used PRISMA guidelines to identify all original published and unpublished experiments testing the effects of exogenous oxytocin on energy intake in wild-type animals and in humans, where oxytocin was administered in the absence of other active drugs or surgeries. Following this, we then identified subsets of experimental designs conducive to synthesis by quantitative meta-analysis. We also aimed to identify relevant moderators of oxytocin's effects on feeding in order to clarify the conditions under which these anorexigenic effects hold.

Methods

Search Strategy and Eligibility Criteria

Two of the authors conducted a systematic literature search to identify original studies which had administered exogenous oxytocin to either animals or humans, and compared its effects on energy intake with a placebo condition. This search was conducted following PRISMA guidelines ¹⁴. We followed reporting guidelines suggested by de Vries and colleagues for pre-clinical intervention studies in the data extraction and reporting methods described below ¹⁵.

The search terms included in the literature search were: “oxytocin” AND (“feed*” OR “food” OR “eat” OR “consum*” OR “intake” OR “hunger” OR “satiety” OR “appetite” OR “meal”). The eligibility criteria for studies included in the systematic review are as follows:

Inclusion criteria:

- Original experiment
- Independent variable: Administration of exogenous oxytocin compared to placebo
- Dependent variable: Quantity of food or nutritive substance consumed
- Oxytocin administered in isolation from any other drug or neural stimulation
- Article available in English

- Neurologically typical participants (e.g., participants with Prader-Willi Syndrome were excluded)

Exclusion criteria:

- Studies testing consumption of alcohol/ethanol or methamphetamines
- Studies testing consumption of plain water, saccharin, or sodium solutions
- Studies of breastfeeding neonates
- Studies measuring oxytocin's effect on conditioned taste aversion

In March 2016, these terms were included in a title or topic search in the Web of Science (Core Collection) and in a text word search in PubMed. In November 2016, these same search terms were entered into a literature search using the following Ovid resources: International Pharmaceutical Abstracts, Ovid MEDLINE(R) I-Process & Other Non-Indexed Citations, Ovid MEDLINE R, PsycArticles Full Text, PsycInfo, Ovid MEDLINE(R) Epub Ahead of Print. The PubMed and Web of Science searches were then updated by the first authors in December 2016.

The first author then proceeded to screen the reference lists of relevant reviews in order to identify articles not included in the main search results, and independently contacted authors known to have unpublished eligible studies (identified through individual correspondence, conference attendance, and reference to unpublished data within a published paper). In March 2017, the second author repeated the literature search among the same databases. The first and second authors discussed discrepancies among the identified search results until a consensus regarding each article's eligibility was reached. The literature search was once again updated using the same databases in July 2017. Basic study characteristics (including sample information, dose of oxytocin administration, and duration of feeding

measurement) and a qualitative summary of each experiment's findings were extracted by a single author.

Meta-Regression

Given the wide variety of studies identified by the systematic literature search, we opted to conduct five separate meta-regressions in order to maximize the homogeneity within each analysis. The five meta-regressions were then conducted amongst each of the following sets of experiment: 1) single-dose animal studies measuring feeding over one hour after a central injection of oxytocin; 2) single-dose animal studies measuring feeding over one hour after systemic administration of oxytocin; 3) chronic-dosing animal studies administering central injections of oxytocin; 4) chronic-dosing animal studies administering systemic injections of oxytocin; 5) human studies. Effect size data (including raw means and standard deviation or standard error) and sample sizes for each study were necessary for each eligible study to be included in a meta-regression. These data were extracted by a single author directly from tables or text within the paper in cases where they were reported. For papers in which these data were not reported, the authors of the paper were contacted with a request for this information via e-mail, or via Research Gate where a current valid e-mail address was unavailable. Where these data were unavailable, the eligible paper has been described in the results of the systematic review, but omitted from the meta-regression by necessity.

As not all of the studies identified in original systematic review were eligible for inclusion in one of these meta-regressions, the full findings of each study included in the systematic review have been reported in separate tables. The moderating and mediating factors influencing oxytocin's effects on energy intake have been summarized in a qualitative synthesis, which follows the quantitative results reported below.

Each meta-regression was conducted as a random-effects multi-level analysis with autoregressive structure, where the second-level corresponded to a specific sample of test

subjects. The meta-regressions' results are reported in terms of the standardized mean difference between placebo and oxytocin conditions. The meta-regressions were conducted using the `escalc` and `rma.mv` commands in the `metafor` package for R¹⁶. The forest plots and bias plots were generated using the Comprehensive Meta-Analysis software. In four experiments within the meta-analysis for human studies, the within-subject correlation was not available. The average within-subject correlation for human studies (0.61) was therefore imputed for these experiments.

Results

Systematic Review

The quantity of papers identified and screened at each step of the PRISMA process during the original systematic literature search is presented in Figure 1. Two additional unique papers were identified through the updated literature search, and one additional paper was identified through author correspondence. The original and updated literature searches together identified a total of 57 relevant papers.

Forty-seven papers included at least one experiment that measured the effects of a single dose of oxytocin on feeding. The 114 experiments measuring the effects of a single dose of oxytocin are summarized in Supplementary Table 1. Eighteen papers included at least one experiment that administered chronic dosing of oxytocin. The 56 experiments measuring the effects of chronic oxytocin dosing on feeding are summarized in Supplementary Table 2.

Meta-Regression

Acute central animal studies. We first conducted the meta-regression for the studies that administered oxytocin centrally, entering moderators for Dose and Body Mass. As all animals were male and housed individually, we did not include moderators for gender or socialization. The Cook's plot generated by this analysis revealed that one study (Arletti et

al., 1989¹, Experiment 2a) yielded undue influence on the results. This study was therefore excluded from the final analysis, resulting in a total of nine experiments with a pooled sample size of 150 observations. (Note: as several studies incorporated a within-subjects design and/or repeated experiments using the same animals, the number of total observations does not equal the total number of subjects.) The final analysis found a significant main effect of oxytocin, showing that a single dose of centrally-administered oxytocin reduced feeding with a large effect size ($d = -1.26$, $SE = 0.451$, $p = 0.005$, 95% CI [-2.149, -0.380]). The forest plot for this meta-regression is shown in Figure 2. Neither of the included moderators was significant: Dose (estimate = -0.003, $SE = 0.017$, $p = 0.857$, 95% CI [-0.036, 0.030]); Body Mass (estimate = 0.000, $SE = 0.000$, $p = .315$, 95% CI [-0.000, 0.000]). There was significant residual heterogeneity: $Q(8) = 22.94$, $p = 0.003$. There was significant residual heterogeneity after controlling for Dose ($QE(7) = 22.94$, $p = 0.002$ and Body Mass $QE(7) = 20.49$, $p = 0.005$).

Acute systemic animal studies. We next repeated the analysis for studies administering a single dose of systemic oxytocin including moderation analyses for Gender, Dose, and Body Mass. This meta-regression included findings from 26 experiments and 510 observations. All animals were individually housed; therefore, socialization was not entered as a moderator. Visual inspection of the Cook's plot did not reveal undue influence of any study (all values < 0.12). This analysis for single-dose studies administering oxytocin systemically also found that oxytocin significantly reduced feeding with a large effect size ($d = -1.17$, $SE = 0.307$, $p < .001$, 95% CI [-1.776, -0.574]). There was significant heterogeneity in the results: $Q(25) = 188.38$, $p < .001$. The moderation analyses revealed a small dose-response effect (estimate = -0.002, $SE = 0.0005$, $p < .0001$, 95% CI [-0.003, -0.001]). The forest plot for this meta-regression is shown in Figure 3. Neither of the other included moderators were significant: Gender (estimate = 0.48, $SE = 1.220$, $p = .694$, 95% CI [-1.912,

2.872]); Body Mass (estimate = 0.008, $SE = 0.005$, $p = .091$, 95% CI [-0.001, 0.017]). There was significant residual heterogeneity after controlling for each moderator: Dose ($QE(d24) = 104.31$, $p < .001$); Gender ($QE(24) = 187.81$, $p < .001$); Body Mass ($QE(24) = 131.74$, $p < .001$).

Chronic central animal studies. For the meta-regression of animal studies administering repeated central injections of oxytocin we entered the following moderators: Gender, Dose, Body Mass, and Duration of Oxytocin Administration. The quantity of energy intake on the final day of feeding measurement was compared between oxytocin and placebo conditions. Data were drawn from 20 experiments with a total of 349 observations. As all animals were housed alone, socialization was not included as a potential moderator. Visual inspection of the Cook's plot did not reveal undue influence of any study (all values < 0.30). This analysis did not find a significant main effect of oxytocin on feeding when administered centrally in chronic infusions ($d = 0.15$, $SE = 0.171$, $p = .379$, 95% CI [-0.185, 0.485]). The forest plot for this meta-regression is shown in Figure 4. There was significant heterogeneity: $Q(19) = 43.08$, $p = 0.001$. None of the included moderators were significant, and there was significant residual heterogeneity after controlling for each moderator. The results of all moderation analyses are presented in Table 1.

Chronic systemic animal studies. The same analysis was then repeated for animal studies that administered chronic infusions of oxytocin systemically. The quantity of energy intake on the final day of feeding measurement was compared between oxytocin and placebo conditions. Seventeen experiments with a total of 255 observations were included in this meta-regression. We entered the following moderators: Gender, Dose, Body Mass, Duration of Administration, and Social Condition. Visual inspection of the Cook's plot did not reveal undue influence of any study (all values < 0.90). Again, we did not find a significant main effect of oxytocin on feeding ($d = -1.52$, $SE = 0.963$, $p = .115$, 95% CI [-3.407, 0.369]). The

forest plot for this meta-regression is shown in Figure 5. The moderators Gender, Dose, and Duration of Administration were significant. Oxytocin had a significantly greater anorexigenic effect in males, and the inhibitory effect of oxytocin on feeding decreased in magnitude over time. The results for dose indicated a reverse dose-response effect, such that greater dose was associated with less inhibition of oxytocin on feeding; however, the effect size was close to zero (estimate = 0.0002, SE = 0.0001, $p = 0.039$, 95% CI [0.0000, 0.0003]). There was significant heterogeneity in study results ($Q(22) = 206.88$, $p < .001$) and significant residual heterogeneity after controlling for each moderator. The results of all other moderator analyses are reported in Table 2.

Human studies. The meta-regression for human studies included 21 experiments with a total of 1020 observations. We entered the following moderators: Liquid-versus-Solid Food, Gender, Dosage, Fasted-versus-Full condition, Duration of Feeding, and Diagnosis. Visual inspection of the Cook's plot did not reveal undue influence of any study (all values < 0.8). This analysis did not find a significant main effect of oxytocin on feeding (estimate = -0.10, SE = 0.075, $p = 0.194$, 95% CI [-0.245, 0.050]). The forest plot for this analysis is shown in Figure 6.

There was significant heterogeneity between studies: $Q(df = 20) = 55.82$, $p < .001$. All moderators except for Dose and Diagnosis were found to be significant (results shown in Table 3). Oxytocin reduced feeding to a greater degree for solid, rather than liquid foods (e.g., nutrient drinks, juice and smoothies). There was a greater inhibitory effect of oxytocin on feeding for males than females, when participants were full, rather than fasted, and when food was presented for a longer period of time (although the effect size was close to zero). There was a marginally significant effect such that oxytocin reduced feeding to a greater degree in obese participants. A greater dose of oxytocin was not associated with quantity of

food consumption. There was significant residual heterogeneity after taking each moderator into account. Residual heterogeneity for each moderator is reported in Table 3.

Based on the difficulty of interpreting the results given such a range of significant moderators, we then proceeded to repeat the analysis including only studies that had measured the consumption of solid foods. As all but one of the studies in the meta-regression for solid foods included only female participants, the gender moderator was not included in this analysis.

Ten experiments with a total of 486 observations were included in the meta-regression for human studies measuring consumption of solid foods. Visual inspection of the Cook's plot did not reveal undue influence of any study (all values < 0.7). The meta-regression for human studies isolated into the solid food condition found a marginally significant main effect of oxytocin on food consumption with a small effect size ($d = -0.25$, $SE = 0.132$, $p = 0.055$, 95% CI $[-0.510, 0.006]$). The forest plot for this meta-regression is shown in Figure 7. None of the included moderators were significant (results shown in Table 4). There was significant residual heterogeneity after controlling for Gender, Fasted or Full condition, Duration of Administration, and Dose. Although the diagnosis moderator was not significant ($Q_m(3) = 3.01$, $p = 0.391$), there was no longer significant residual heterogeneity after controlling for diagnosis ($Q_E(6) = 12.18$, $p = .058$).

Publication Bias. The funnel plots associated with each meta-regression are shown in Supplementary Figures 1-5. The funnel plots indicated that most studies had a moderate degree of precision, with a broad range of effect sizes reported. These findings do not suggest systematic publication bias towards paper with either strong or weak effect size.

Mediators and Moderators of Oxytocin's Anorexigenic Effects

Among the systematic review, there were many factors that were found to moderate the effect of oxytocin on feeding in some studies, including: sex of the animal, pregnancy,

dose, method of administration, setting, and dietary factors. As not all studies met criteria for inclusion in one of the meta-regressions, the following reported results will focus on a sample of other identified studies that examined a moderating or mediating factor in a controlled experimental design.

Sex differences. Several studies investigated sex differences in oxytocin's effects on feeding. Bjorkstrand and Uvnas-Moberg ¹⁷ found that a 5µg intracerebroventricular injection of oxytocin increased feeding in female, but not male rats. Conversely, Zhou, Ghee, See and Reichel ¹⁸ found that oxytocin induced a greater reduction in feeding in female rats, with anorexigenic effects observed at 0.3, 1, and 3mg/kg doses of oxytocin, while only the 3mg/kg dose was effective at reducing feeding in males. To further add to these mixed findings, Benelli, Bertolini and Arletti ¹⁹ failed to find any differences in male versus female rats' response to oxytocin's effects on feeding. Previous studies have demonstrated that feeding varies across differing stages of the oestrous cycle in rodents, non-human primates, and humans ²⁰⁻²². The feeding response to hunger-related hormones (including ghrelin) and neurosteroids also varies throughout different stages of the estrous cycle in female rats ²³. It is recommended that future studies continue to investigate the extent to which estrous cycle phase and fluctuations in ovarian hormones may influence the satiety response to oxytocin in female animal models.

Pregnancy. Only one study ²⁴ tested the effect of pregnancy as a moderator for oxytocin's effect on feeding. This study identified that 1µg intracerebroventricular injection decreased feeding in virgin female rats over one hour of measurement, while having no continued effect on feeding over 12 hours. However, a different pattern of effects was observed in pregnant rats, with the same dose of oxytocin exerting no effect on feeding over one hour, while increasing feeding over 12 hours. The authors have proposed that this may be

due to changes in the expression and binding affinity of central oxytocin receptors during pregnancy ²⁴.

Dose and method of administration. Most studies testing a dose-response effect of oxytocin found that greater doses of oxytocin were associated with correspondingly lower levels of subsequent feeding. The minimum effective dose required to observe anorexigenic effects of oxytocin depended on the method of administration, with central injections of oxytocin requiring much lower doses than peripheral injections.

Findings of note include that of Ong, Alhadeff and Grill ²⁵, who reported that a 1µg/1µL dose of oxytocin injected into the fourth ventricle reduces feeding over 30 minutes only when a dietary preload had been provided, and did not continue to affect feeding over 1.5 hours. By contrast, a 0.3µg dose of oxytocin injected into the nucleus of the solitary tract (NTS) was found to significantly reduced feeding over 30 minutes regardless of whether a dietary preload had been provided. This inhibitory effect on feeding persisted over 1.5 hours in the dietary preload condition. These findings seem to point to greater sensitivity to oxytocin's effects on feeding within the NTS than within hindbrain receptors accessed via fourth cerebral ventricle, suggesting that the NTS may represent a more proximal site mediating oxytocin's effects on feeding. However, these results contradict those found by Ho and colleagues ²⁶, who reported that oxytocin injection into the fourth ventricle was effective at reducing feeding in the absence of a preload at a dose of 1µg. The differential sensitivity of the NTS and fourth ventricle to oxytocin's anorexigenic effects is therefore a question that would be interesting for future research to explore.

In another study examining the impact of injecting oxytocin into different regions of the central nervous system, Herisson, Waas, Fredriksson, Schioth, Levine and Olszewski ²⁷ demonstrated that 1µg and 3µg doses of oxytocin injected directly into the nucleus accumbens core reduces both chow intake and the consumption of a 10% sucrose solution in

male rats, while these inhibitory effects are not observed when the same dose is injected into the nucleus accumbens shell. The administration of oxytocin into the nucleus accumbens core was associated with increased Fos-immunoreactivity in both the nucleus accumbens core itself, as well as the paraventricular nucleus and supraoptic nucleus of the hypothalamus: two regions dense in oxytocin neurons and receptors which are involved in feeding regulation ²⁸. These findings therefore support a potential role of the nucleus accumbens core in mediating oxytocin's anorexigenic effects, which does not extend to the nucleus accumbens shell.

One point to note, however, are that most studies administered high supraphysiologic doses of oxytocin. While these doses may be required in the case of peripheral administration to increase the chances that some oxytocin will cross the blood-brain barrier, it ought to be noted that these findings may reflect partial oxytocin binding with vasopressin receptors at high doses that would not occur at physiological levels.

Social setting. The social conditions in which animals were housed was also found to impact the effect of oxytocin on feeding. Grippo, Trahanas, Zimmerman, Porges and Carter ²⁹ found that isolating female prairie voles from litter-mates resulted in a decrease in sucrose intake over a period of two weeks in a placebo condition, but that this effect was prevented by oxytocin. In the co-housed group of prairie voles, however, there were no changes in sucrose intake over time, or any differences between the oxytocin and placebo conditions. Additionally, Herisson, Waas ²⁷ found that central oxytocin administration reduced food and sucrose intake in individually-housed male rats, while neither of these effects were observed in male rats allowed some social contact with a conspecific. Both of these studies point to the potential for social housing to prevent oxytocinergic reductions in feeding that would otherwise occur in isolated social settings.

Dietary factors. Finally, diet-induced obesity was also identified as an important moderating factor for oxytocin's effects on feeding in both animals and humans ^{8, 30-34}. On the

whole, direct comparisons of lean animals consuming standard chow with diet-induced obese animals consuming high-fat diets found that oxytocin had more consistent inhibitory effects on feeding in the dietary-induced obese animals ^{8, 31}. Blevins and colleagues have shown that this moderating effect persists in high fat diet-fed rats, even when matched for body mass and adiposity with chow-fed controls ³¹, thus indicating that this moderating effect may be more attributable to the fat-content of the animal's diet than body composition.

Discussion

This review aimed to identify published and unpublished studies testing the effects of exogenous oxytocin on energy intake in wild-type animals and humans, where oxytocin was administered in isolation from other active drugs and surgery. The systematic review and meta-analysis revealed a robust inhibitory effect of oxytocin on energy intake when administered as a single dose in animals, regardless of whether it was administered via a central or peripheral route. Additionally, while several individual experiments did show a continued inhibitory effect of oxytocin for periods of two or more weeks in rats and mice ^{8, 31, 35-39}, when final-day energy intake was compared between placebo and oxytocin conditions in the quantitative meta-analysis this inhibitory effect did not hold, despite a trend towards inhibition in studies administering oxytocin systemically.

The human studies did not find a main effect of oxytocin on energy intake; however, there was found to be a trend towards a decrease in the consumption of solid foods induced by oxytocin. Additionally, oxytocin had a stronger inhibitory effect on energy intake in male participants, in obese participants, and when participants completed the experiment in the full condition (rather than fasted condition). The specific finding that oxytocin reduced feeding to a greater degree in obese humans ³⁰ is consistent with findings from animal studies, which have also indicated a greater anorexigenic effect in diet-induced obese mice and rats ⁸.

The moderating effect of liquid versus solid foods was unexpected amongst human studies, particularly given previous animal research demonstrating the inhibitory effect of oxytocin on the consumption of palatable liquid solutions ^{27, 40, 41}. The mechanism driving the difference between oxytocin's effect on liquid and solid foods is unclear. One hypothesis is that oxytocin may reduce gastric motility, thus contributing to the sensation of satiety as solid food remains in the gut for a longer period of time. This hypothesis is supported by research demonstrating that oxytocin can reduce gastric motility in rats ⁴²⁻⁴⁵ and mice ⁴⁶. However, Borg and colleagues have found evidence to the contrary, indicating that oxytocin does not affect gastric emptying rate in humans following consumption of a liquid meal ⁴⁷. Further research would be useful to test this hypothesis as it pertains to solid foods, and to further investigate the reasons for oxytocin's greater inhibitory effect for solid, versus liquid, consumption in humans.

The pattern for the inhibitory effect of oxytocin on feeding to decrease over time was reflected in a significant moderator analysis carried out for the meta-regression of studies that administered systemic oxytocin to animals chronically over time. This meta-regression, as well as the meta-regression for human studies, were also significantly moderated by sex, such that the effects of oxytocin on reducing feeding were significantly greater for male animals. This overall moderating effect of sex across studies included in the meta-regression is interesting to observe given the highly mixed findings regarding sex differences reported in individual studies ¹⁷⁻¹⁹. A greater density of oxytocin receptors has previously been reported within the spinal cord and ventromedial hypothalamus of male rats ⁴⁸, which may potentially explain the greater sensitivity to oxytocin's anorexigenic effects in males. However, the activity of oxytocin and oxytocin receptors also varies across stages of the follicular cycle in female prairie voles ⁴⁹. Furthermore, it is known that levels of endogenous plasma oxytocin vary across stages of the menstrual cycle in humans ⁵⁰. One can hypothesize that this natural

variation may moderate the effects of exogenously-administered oxytocin. Variation in the follicular stage at which oxytocin was administered to female animals may therefore partially account for mixed findings reported for feeding effects in previous studies. It would therefore be useful to specifically investigate variation in oxytocin's effect on feeding across different phases of the follicular cycle, and associated variation in plasma levels of other hormones (e.g., oestrogen).

In terms of the mechanisms explaining oxytocin's greater effect in obese animals and humans, it is known that oxytocin receptors exhibit a higher-affinity binding state in the presence of cholesterol ⁵¹. Therefore, it may be that a greater fat- and cholesterol-rich diet at least partially explains the greater anorexigenic effects of oxytocin observed in obese animals and humans.

The mechanisms and neural circuits explaining the overall anorexigenic effects of oxytocin are still somewhat uncertain. Oxytocin is known to mediate the anorexigenic effects of cholecystikinin (CCK), which acts on oxytocin neurons via vagal afferents from the gut ². This finding has received further support from research demonstrating that injections of oxytocin into the third cerebral ventricle enhance the anorexigenic effects of low doses of CCK-8 ³¹ while, conversely, pre-treatment of an oxytocin receptor antagonist into the fourth ventricle suppresses the anorexigenic effects of CCK ^{52, 53}. In addition to this role mediating the effects of CCK, oxytocin has also been implicated in mediating leptin's ^{54, 55} and nesfatin-1's ⁵⁶ inhibitory effects on food intake. The downstream mechanisms by which oxytocin impacts on feeding; however, are less certain.

It is likely that central and peripheral oxytocin exert effects of feeding via different mechanisms. Previous research has identified that only approximately 0.002% of peripheral oxytocin crosses the blood-brain barrier where it might access central receptors ⁵⁷. However, the extent to which peripheral oxytocin exerts its effects via central versus peripheral

receptors, such as those in the gut ⁵⁸, may be species-dependent. In mice, the literature supports a role for vagal afferent nerves in mediating the anorexigenic effect of peripheral oxytocin ^{59,60}. This interpretation draws support from research finding that oxytocin receptors are expressed in the nodose ganglion of the vagus nerve ⁵⁹, as well as further research that has gone on to demonstrate that vagotomy results in an attenuation of the anorexigenic effect of peripherally-administered oxytocin in mice ⁶⁰. In rats, however, Ho and colleagues ²⁶ have demonstrated that hindbrain receptors accessed via the fourth ventricle are predominantly responsible for mediating the inhibitory effects of peripheral oxytocin on feeding. Further research clarifying which pathway/s predominate this mediating effect in primates and humans has not yet been conducted, and would be useful to investigate in future studies.

Brain nuclei including the paraventricular nucleus, NTS, and arcuate nucleus have been implicated as potentially relevant in mediating oxytocin's effects on feeding ^{25, 60-63}. This evidence comes from studies indicating the direct injections of oxytocin into these areas suppresses food intake ^{25,61}, as well as immunohistological studies demonstrating that the Fos activation of oxytocin neurons in these regions co-occurs with the termination of feeding ⁶⁰⁻⁶³. Furthermore, studies have demonstrated that injections of oxytocin directly into the ventral tegmental area, nucleus accumbens core, and ventromedial hypothalamus are effective in inhibiting feeding; thereby indicating that these regions may mediate the anorexigenic effects of oxytocin as well ^{27, 41, 64}. Given that oxytocin is effective in reducing energy intake when administered both centrally and peripherally, it may be the case that oxytocin acts as a central messenger integrating central and peripheral signals. This hypothesis, however, requires further evidence to corroborate.

It has also been proposed that oxytocin may exert inhibitory effects on energy intake via a physiological pathway mediated by reward-based mechanisms ⁶⁵. This hypothesis is lent support by the high density of oxytocin receptors along the pathways connecting the nucleus

accumbens and ventral tegmental area ⁶⁶⁻⁶⁸, two regions known to be highly involved with processing food reward ⁶⁹. Additionally, oxytocin injected directly into the nucleus accumbens has been found to reduce methamphetamine-induced place preference ⁷⁰ and prevent relapse to methamphetamine-seeking behavior after extinction ⁷¹. Together, these findings point to an ability for oxytocin to disrupt reward-related processing in these regions, which may additionally extend to suppressing reward-based feeding behaviour. This hypothesis, if true, may also explain the stronger effects of oxytocin in reducing hedonic, as opposed to hunger-driven, feeding in human studies ^{30, 72, 73}. Further research in animals and humans would be useful to test this hypothesis further, and elucidate the precise mechanisms of oxytocin's acute action on energy intake.

The confirmation of oxytocin's anorexigenic effects when administered as a single dose echoes conventional understanding in the literature, while highlighting the limits of this effect: such as the reverse (orexigenic) effect observed in pregnancy ²⁴ and when socially-housed animals subsequently undergo separation from litter-mates ²⁹. The null findings revealed in the meta-analysis testing the chronic effects of oxytocin on feeding are disappointing in the context of potential hopes for developing oxytocin supplementation as a new treatment for binge-type eating disorders in humans, and conflict with individuals studies which have reported the persistence of oxytocin's anorexigenic effects over two to three weeks of measurement in rats and mice ^{8, 31, 36, 38, 74, 75}, and for two weeks post-treatment in rhesus monkeys ³⁹. It may be the case that a regime of intermittent oxytocin administration would result in the same anorexigenic effects observed within the course of a single experimental administration, without resulting in the same degree of receptor adaptations. Future research testing different temporal regimes of oxytocin administration is recommended to test this hypothesis.

The diminishing effects of oxytocin are in keeping with the results arising from individual studies making use of the repeated administration of oxytocin^{8, 31, 33, 36, 37} or an oxytocin agonist⁷⁶. These findings also concord with social experiments which have found that the anxiolytic effects of oxytocin disappear or reverse over time⁷⁷. Peters et al. found that the reversal of acute anxiolytic effects over chronic dosing was associated with a concurrent reduction in oxytocin receptor binding. Indeed, previous work has shown that oxytocin receptor binding can reduce by as much as 50% over 10 days of chronic administration, driven largely by down-regulation of the oxytocin receptor⁷⁸. It is therefore likely that this reduced binding potential may explain the dampening of oxytocin's effects on feeding.

The null findings generated from the meta-regressions of chronically-administered oxytocin studies should be interpreted with some degree of caution. Although the final-day analyses used for the meta-regressions maximized the number of commensurable studies eligible for inclusion, it may be that noise in the data on the final day data masked smaller effects identified by studies that compared average consumption across several days. It should also be noted that the scope of the current review is limited to oxytocin's effects on energy intake alone, and that oxytocin's effects on other metabolic parameters deterring obesity (e.g., lipolysis, brown adipose tissue thermogenesis, and energy expenditure) may persist with chronic administration⁷⁴.

Limitations of the current review include some inherent drawbacks of the methodology chosen for the meta-regressions. We aimed to reach a compromise between maximizing homogeneity of studies included in the meta-regression, while also including the maximum number of experiments. The choice to therefore include only single-dose studies that measured the effects of oxytocin over one hour of feeding therefore constrained these meta-regressions to a reasonable scope and similar effect size. Differences in the exact

location of administration and animals included in each experiment, however, may have added to the heterogeneity of effect size observed across studies. Furthermore, the current systematic review did not include findings from non-wild-type animals (e.g., Sim-haploinsufficient rats and mice) or animals whose nervous systems were altered by surgery or direct stimulation. Therefore, although the current findings reveal the effects of exogenous oxytocin in wild-type animals, it should be noted that there are further findings reflecting the implication of oxytocin on feeding that were not included within the scope of the present review.

Regarding the clinical implications of these findings, it is particularly encouraging to have observed that the anorexigenic effects of oxytocin were stronger for populations that suffer from over-eating and binge-eating. These findings suggest that, in the short term, oxytocin may reduce the likelihood of binge-eating and overeating for populations with obesity, bulimia nervosa, and binge eating disorder. However, the null findings from the meta-regressions of chronic animal studies cast doubt on the persistence of oxytocin's acute effects. Testing different dosing schedules of oxytocin would be useful for identifying a potential frequency and dose of administration that maintains oxytocin's beneficial effects over time, without resulting in the reduction of receptor binding.

In conclusion, the current systematic review has confirmed the anorexigenic effect of a single dose of oxytocin in animals first documented by the Arletti lab ¹, while demonstrating that this anorexigenic effect does not persist throughout chronic dosing. There was a trend for intranasal oxytocin to reduce feeding in humans, and this effect was stronger for individuals with obesity, bulimia nervosa, and binge eating disorder. Future research is needed to further elucidate the mechanisms of these effects, and whether differing dosing schedules might prevent their attenuation with chronic administration.

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Tables and Figures

Figure 1. PRISMA flow diagram for the original systematic literature search

Figure 2. Forest plot of studies measuring the effect of a single-dose of central oxytocin on energy intake over a one-hour measurement duration in animals. RLCV = right lateral cerebral ventricle; 4V = fourth cerebral ventricle; VMH = ventromedial hypothalamus; ICV = intracerebroventricular.

Figure 3. Forest plot of studies measuring the effect of a single-dose of systemic oxytocin on energy intake over a one-hour measurement duration in animals.

Figure 4. Forest plot of studies measuring the effect of chronic dosing of central oxytocin on energy intake in animals. ICV = intracerebroventricular; 3V = third cerebral ventricle; 4V = fourth cerebral ventricle.

Figure 5. Forest plot of studies measuring the effect of chronic dosing of systemic oxytocin on energy intake in animals.

Figure 6. Forest plot of studies measuring the effect of a single-dose of intranasal oxytocin on energy intake in humans.

Figure 7. Forest plot of studies measuring the effect of a single-dose of intranasal oxytocin on solid food intake in humans.

Table 1: Results of Moderator Analyses for Chronic Central Animal Studies

* $p < .05$; *** $p < .001$.

Table 2: Results of Moderator Analyses for Chronic Systemic Animal Studies

* $p < 0.05$.

Table 3: Results of Moderator Analyses for All Human Studies

* $p < .05$; ** $p < .01$; *** $p < .001$.

Table 4: Results of Moderator Analyses for Human Studies Measuring Solid Food Intake

Supplementary Table 1: Summary of studies administering a single dose of oxytocin

Note. AcbC = nucleus accumbens core; AcbSh = nucleus accumbens shell; NTS = nucleus of the solitary tract. Seventy-one of these experiments found that oxytocin reduced feeding for at least one time point measured, 39 experiments found no effect of oxytocin on feeding, and 4 experiments found that a single dose of oxytocin increased feeding.

Supplementary Table 2: *Summary of studies administering chronic oxytocin treatment*

Note. Twenty-seven experiments found that oxytocin reduced feeding at some point following at least 3 days of treatment, 27 found no significant effects of oxytocin on feeding, and 2 found that chronic dosing of oxytocin increased feeding

Supplementary Figure 1. Funnel bias plot for animal studies administering a single-dose of central oxytocin.

Supplementary Figure 2. Funnel bias plot for animal studies administering a single-dose of systemic oxytocin.

Supplementary Figure 3. Funnel bias plot for animal studies administering chronic central oxytocin.

Supplementary Figure 4. Funnel bias plot for animal studies administering chronic systemic oxytocin.

Supplementary Figure 5. Funnel bias plot for human studies measuring the effect of intranasal oxytocin on energy intake.